

# **EXHIBIT 10**

# **Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry**

**U.S. Department of Health and Human Services  
Food and Drug Administration  
Center for Drug Evaluation and Research (CDER)  
Center for Biologics Evaluation and Research (CBER)**

**July 2019  
Drug Safety**

**Revision 1**

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# **Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry**

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*Contains Nonbinding Recommendations*

## **Risk Evaluation and Mitigation Strategies: Modifications and Revisions Guidance for Industry<sup>1</sup>**

This guidance represents the current thinking of the Food and Drug Administration (FDA or Agency) on this topic. It does not establish any rights for any person and is not binding on FDA or the public. You can use an alternative approach if it satisfies the requirements of the applicable statutes and regulations. To discuss an alternative approach, contact the FDA office responsible for this guidance as listed on the title page.

### **I. INTRODUCTION**

This guidance provides information on how the FDA defines the types of changes to approved risk evaluation and mitigation strategies (REMS), how application holders<sup>2</sup> should submit changes to an approved REMS,<sup>3</sup> and how the FDA will process submissions from application holders for changes to REMS. Specifically, this guidance provides information, as described in section 505-1(h) of the Federal Food, Drug, and Cosmetic Act (FD&C Act), on what types of changes to REMS will be considered *modifications* of the REMS and what types of changes will be considered *revisions* of the REMS (changes that may be implemented following notification to the FDA).<sup>4</sup> This guidance is issued pursuant to section 505-1(h)(2)(A)(ii), (iii), and (iv) of the FD&C Act and section 1132(c) of Public Law 112-144.

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<sup>1</sup> This guidance has been prepared by the Office of New Drugs, the Office of Surveillance and Epidemiology, and the Office of Compliance in the Center for Drug Evaluation and Research (CDER) in cooperation with the Center for Biologics Evaluation and Research at the Food and Drug Administration.

<sup>2</sup> Under section 505-1(b)(7) of the Federal Food, Drug, and Cosmetic Act, the term *responsible person* means “the person submitting a covered application or the holder of the approved such application.” For ease of reference, this guidance refers to a responsible person as an *application holder*.

<sup>3</sup> The REMS is the enforceable document that describes the elements that an application holder is required to implement to mitigate a specific, serious risk listed in the labeling of the drug. All proposed materials that are included as part of the REMS (e.g., communication and educational materials, Medication Guide, patient package insert, enrollment forms, prescriber and patient agreements) are also approved, and are appended to the REMS document. This guidance refers to these materials as *REMS materials*.

<sup>4</sup> See 21 U.S.C. 355-1(h)(2)(A) and P.L. 112-144, §1132(c).

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This guidance applies to all types of REMS, including REMS that are part of a shared system (SS REMS).<sup>5,6</sup>

This guidance does not address additional submission procedures that may apply to application holders proposing changes to REMS that are part of a shared system and that use a drug master file (DMF) for their REMS submissions.<sup>7</sup>

This guidance is being issued consistent with the FDA's good guidance practices regulation (21 CFR 10.115). The guidance represents the Agency's current thinking on changes to REMS. It does not create or confer any rights for or on any person and does not operate to bind FDA or the public.

## **II. BACKGROUND**

A REMS is a required risk management plan that uses tools beyond the prescribing information (the package insert) to ensure that the benefits of certain drugs outweigh their risks.<sup>8</sup> If the FDA determines that a REMS is necessary to ensure that the benefits of a drug outweigh its risks, the FDA is authorized to require a REMS for such drugs under section 505-1 of the FD&C Act.<sup>9</sup> Section 505-1(g) and (h) includes provisions regarding the assessment and modification of an approved REMS.

An application holder may propose a REMS modification at any time. In addition, when the FDA determines that a modification of a REMS is necessary to ensure that the benefits of a drug outweigh its risks or to minimize the burden on the health care delivery system of complying with the REMS, the FDA has the authority to require that the application holder submit a proposed modification to a REMS under section 505-1(g) of the FD&C Act.

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<sup>5</sup> For the purposes of this guidance, a *shared system* REMS (SS REMS) is a program that encompasses multiple prescription drugs and is developed and jointly implemented by two or more application holders. An SS REMS includes a single, shared system REMS as defined in section 505-1(i)(1)(B) of the FD&C Act.

<sup>6</sup> See the draft guidance for industry *Development of a Shared System REMS* (June 2018). When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

<sup>7</sup> For submission procedures for changes to SS REMS that use a DMF for their submissions, see the draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions* (November 2017). When final, this guidance will represent the FDA's current thinking on this topic.

<sup>8</sup> For the purposes of this guidance, unless otherwise specified, references to *drugs* include drugs approved under the FD&C Act and biological products licensed under the Public Health Service Act (PHS Act), other than biological products that also meet the definition of a device in section 201(h) of the FD&C Act (21 U.S.C. 321(h)).

<sup>9</sup> Section 505-1 applies to applications for prescription drugs submitted under FD&C Act subsections 505(b) (i.e., new drug applications) or (j) (i.e., abbreviated new drug applications), and applications under section 351 of the PHS Act (i.e., biologics license applications).

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The Food and Drug Administration Safety and Innovation Act (FDASIA) amended the REMS modification provisions under section 505-1(g) and (h) of the FD&C Act. Section 505-1(h), as amended by FDASIA, requires the FDA to review and act on proposed *minor modifications*, as defined in guidance, within 60 days.<sup>10</sup> It also requires the FDA to establish, through guidance, that *certain modifications* can be implemented following notification to the FDA.<sup>11</sup> In addition, section 505-1(h) requires the FDA to review and act on REMS modifications to conform the strategy to approved safety labeling changes, or to a safety labeling change that the FDA has directed the application holder make pursuant to section 505(o)(4) of the FD&C Act, within 60 days.<sup>12</sup> Finally, section 505-1(g)(4)(A) of the FD&C Act as amended by FDASIA specifies that proposed REMS modifications no longer require submission of a REMS assessment; instead, proposed modifications must include an adequate rationale for the proposed changes.

Existing FDA regulations describe how to make changes to approved applications, and include a mechanism for rapid implementation of certain changes.<sup>13</sup> Some changes must be submitted as a prior approval supplement (PAS) and approved before they are implemented. Changes-being-effected (CBE) supplements may be implemented at the time they are submitted or 30 days following submission.<sup>14</sup> If a supplement was inappropriately submitted as a CBE, the FDA will notify the application holder that the proposed change(s) require FDA approval before implementation. A description of how these existing submission requirements apply to proposed REMS changes is provided below in greater detail.

### III. POLICY

Changes to REMS will be categorized as REMS revisions, minor REMS modifications, or major REMS modifications, based on the degree of their potential effect on (1) the information provided in the REMS related to the serious risk(s) associated with the drug; (2) the safe use of the drug; and/or (3) the actions that the application holder, patients, health care providers, and other stakeholders must take to comply with the REMS.

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<sup>10</sup> See section 505-1(h)(2)(A)(ii) of the FD&C Act. Section 1132(c) of FDASIA also provides that the FDA “shall issue guidance that, for purposes of section 505-1(h)(2)(A) of the [FD&C Act], describes the types of modifications to approved risk evaluation and mitigation strategies that shall be considered to be minor modifications of such strategies.”

<sup>11</sup> See section 505-1(h)(2)(A)(iv) of the FD&C Act. The FDA interprets *certain modifications* that can be implemented upon notification to the FDA to be changes to a REMS that are editorial in nature or appropriate for submission in an annual report, and therefore calls these REMS changes *revisions* to differentiate these changes from modifications that require the submission of a supplement and the FDA review and action.

<sup>12</sup> See section 505-1(h)(2)(A)(iii) of the FD&C Act.

<sup>13</sup> See 21 CFR 314.70 and 601.12.

<sup>14</sup> PAS-proposed changes must be approved by the FDA before implementation (21 CFR 314.70(b) and 21 CFR 601.12(b)(3) and (f)(1)). CBE supplements contain changes that may be implemented by the application holder either immediately upon FDA receipt of the supplement (CBE-0 supplements) (21 CFR 314.70(c)(6) and 601.12(c)(5) and (f)(2)(ii)) or 30 days after FDA receipt of the supplement (CBE-30 supplements) (21 CFR 314.70(c) and 601.12(c)(3)).

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Tables 1 through 4 provide examples of REMS revisions and minor and major REMS modifications. These tables are intended to be a representative, rather than comprehensive, list of examples.

**A. REMS Revisions**

REMS revisions are defined as editorial changes that *do not affect*:

- The information contained in the REMS document and/or REMS materials about the serious risk or safe use of the drug
- The actions application holders, patients, health care providers, or other stakeholders must take to comply with the REMS, or the REMS materials that support those actions

Examples of REMS revisions are provided in Table 1.

**Table 1. REMS Revisions (Submitted as REMS Revisions and Summarized in the Annual Report)<sup>15</sup>**

<b>Examples<sup>a</sup></b>
<ul style="list-style-type: none"> <li>• Changes in the application holder name or address to reflect transfer of application ownership<sup>b</sup></li> </ul>
<ul style="list-style-type: none"> <li>• Updates to the application holder's contact information (e.g., mailing address, telephone number, fax number, and/or email address)</li> </ul>
<ul style="list-style-type: none"> <li>• Editorial changes, such as:               <ul style="list-style-type: none"> <li>– Changes in International Classification of Diseases code(s) in the REMS materials or on the REMS website</li> <li>– Changes to the application holder's internal tracking information (e.g., tracking numbers) on REMS forms</li> <li>– Changing the application holder's signatory for a Dear Health Care Provider Letter that is part of the REMS materials</li> <li>– Changing a trademark symbol, designated by <sup>TM</sup>, to the registered trademark symbol, designated by <sup>®</sup></li> <li>– Changes to the approved package count configuration that result in changes to the REMS materials (e.g., a change in the national drug code number(s))</li> </ul> </li> </ul>

*continued*

<sup>15</sup> See section IV., Submission Procedures.



***Contains Nonbinding Recommendations****Table 1, continued*

<b>Examples<sup>a</sup></b>
<ul style="list-style-type: none"> <li>Correction of grammatical, formatting, and/or typographical errors, for example:  <i>“[DRUG] <del>are</del> <u>is</u> associated with the potential <del>risk</del>-risks of seizure and hepatotoxicity.”</i>  <i>“Health care <del>providers</del> <u>providers</u> who prescribe [DRUG] must be <del>specally</del> <u>specialy</u> certified.”</i></li> </ul>
<ul style="list-style-type: none"> <li>The following changes to a Medication Guide that is an element of a REMS:<sup>c</sup> <ul style="list-style-type: none"> <li>Changes in the application holder’s name and/or place of business<sup>d</sup></li> <li>Insertions of the date of the most recent revision of the Medication Guide<sup>e</sup></li> <li>Addition of the side effects statement and toll-free number for reporting adverse events to a Medication Guide<sup>f</sup></li> </ul> </li> </ul>

<sup>a</sup> The types of REMS changes in *italic font* are provided for illustrative proposes. Additions are noted by underline and deletions are noted by ~~striketrough~~.

<sup>b</sup> Application holders are responsible for reporting a transfer of ownership in accordance with Federal regulations. The FDA must be notified in writing by the new and former application holders at the time of transfer in ownership of a new drug application (NDA), abbreviated new drug application (ANDA), or biologics license application (BLA) (21 CFR 314.72; 21 CFR 601.12(f)(1)).

<sup>c</sup> See 21 CFR 314.70(b)(2)(v)(B) for NDAs and 21 CFR 601.12(f)(3)(C) for BLAs.

<sup>d</sup> See 21 CFR 208.20(b)(8)(iii).

<sup>e</sup> See 21 CFR 208.20(b)(8)(iv).

<sup>f</sup> See the guidance for industry *Medication Guides — Adding a Toll-Free Number for Reporting Adverse Events* (June 2009). We update guidances periodically. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

## **B. REMS Modifications**

Proposed REMS modifications are divided into two categories: minor modifications and major modifications.

### *1. Minor REMS Modifications*

Minor REMS modifications are defined as changes that have *a limited effect* on:

- The information contained in the REMS document and/or REMS materials about the serious risk or safe use of the drug
- The actions application holders, patients, health care providers, or other stakeholders must take to comply with the REMS, or on the REMS materials that support those actions

These should be submitted as a CBE-30 supplement (see section IV., Submission Procedures). Examples of minor REMS modifications are provided in Table 2.

*Contains Nonbinding Recommendations***Table 2. Minor REMS Modifications (Submitted as CBE-30 Supplements<sup>16</sup>)**

Type of Change	Examples
Minor modifications that have a <i>limited effect</i> on information contained in the REMS about the serious risk or safe use of the drug	<ul style="list-style-type: none"> <li>• Addition of an approved new strength or dosage regimen of the drug<sup>a</sup></li> <li>• Removal of a strength or dosage form of the drug (other than from the Medication Guide) because either FDA approval has been withdrawn and documented by publication of a <i>Federal Register</i> notice for the strength/dosage form, or the FDA has determined that the strength/dosage form was withdrawn from sale for reasons of safety or effectiveness</li> <li>• Addition of an authorized generic</li> <li>• Adding, removing, or changing information about another drug that is mentioned in the REMS document and/or materials, but is not the drug for which the REMS was required <ul style="list-style-type: none"> <li>– Adding a new, recently approved drug to a class of drugs already mentioned in the REMS materials as having the potential to cause drug-drug interactions</li> </ul> </li> <li>• Adding information previously reviewed and approved for one application that is part of an SS REMS to the REMS document and/or REMS materials for the other applications in the SS REMS <ul style="list-style-type: none"> <li>– Adding a new, recently approved drug in a class to the REMS document and/or REMS materials for the other applications in the SS REMS</li> <li>– Adding new information about an existing drug in a class to the REMS document and/or REMS materials for the other applications in the SS REMS</li> </ul> </li> <li>• Changes to graphics, including changes to the existing manufacturer's logo or the logo for the REMS program</li> </ul>

*continued*<sup>16</sup> See section IV., Submission Procedures.

***Contains Nonbinding Recommendations****Table 2, continued*

Type of Change	Examples
Minor modifications that have a <i>limited effect</i> on the actions application holders, patients, health care providers, and other stakeholders must take to comply with the REMS	<ul style="list-style-type: none"> <li>• Adding a professional society to the list of required recipients of a Dear Health Care Provider Letter required in the REMS materials</li> <li>• Converting an existing prescriber enrollment form into another format to allow for online registration, in addition to paper enrollment via email or fax, without altering the prescriber certification requirements</li> <li>• Creating or converting an existing health care facility enrollment form to allow <i>closed</i> (i.e., self-contained) health care systems to enroll</li> <li>• Changing an existing health care provider or patient enrollment form to collect additional demographic information</li> <li>• Changes to the hours of operation for the REMS call center</li> <li>• Limited changes to the REMS website to improve functionality (ease of use) for stakeholders</li> <li>• Limited changes to the REMS website to clarify current processes required of stakeholders (e.g., changes to clarify how health care providers should navigate the website to complete enrollment in the REMS)</li> <li>• Adding approved REMS materials (new or modified) to the REMS website</li> <li>• Changing the timetable for submission of assessment for REMS involving multiple drugs in the same class and owned by the same application holder to synchronize the assessment due date(s)</li> <li>• Re-ordering the risk information in the REMS materials</li> </ul>

<sup>a</sup> Proposals for a new dose regimen or strength of a drug are submitted as supplemental efficacy or chemistry, manufacturing, and controls (CMC) applications. Proposed REMS modifications submitted or required as part of an efficacy or CMC supplement will be reviewed and acted on as part of that supplement, and not according to the time frames described above for REMS revisions, minor modifications, or major modifications. See section V.F., REMS Modifications Included in Other Submissions.

## 2. *Major REMS Modifications*

Major REMS modifications are defined as changes that have a *substantial effect* on:

- The information contained in the REMS document and/or REMS materials about the serious risk or safe use of the drug
- The actions application holders, patients, health care providers, or other stakeholders must take to comply with the REMS, or the REMS materials that support those actions

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Major REMS modifications include changes to provide new information about the serious risk(s) or safe use of the drug. In addition, modifications to the strategy due to approved safety labeling changes, or to a safety labeling change that the FDA has directed the application holder to make pursuant to section 505(o)(4) of the FD&C Act, are considered major REMS modifications. The FDA interprets REMS modifications that *conform to* safety labeling changes in section 505-1(h)(2)(A)(iii) of the FD&C Act to refer to modifications that transfer the newly approved labeling language into the existing REMS and/or REMS materials. Overall design, programmatic, and/or implementation changes to the REMS that result from approved (or ordered) safety labeling changes are *not considered conforming* REMS modifications.

Examples of major REMS modifications are provided in Tables 3 and 4. Major REMS modifications should be submitted as a PAS (see section IV., Submission Procedures).

**Table 3. Major REMS Modifications (Submitted as a PAS<sup>17</sup>)**

Type of Change	Examples
Major modifications that have a <i>substantial effect</i> on information contained in the REMS about the serious risk or safe use of the drug	<ul style="list-style-type: none"> <li>• Addition, removal, or change to a REMS goal</li> <li>• Addition of new information about the serious risks associated with the drug</li> <li>• Addition of a new indication for use that may alter the serious risks (in relation to benefits) of the drug for the new patient population<sup>a</sup></li> <li>• Addition of new information about drug administration that affects patient safety</li> <li>• Changing the type, frequency, and/or timing of patient laboratory testing required as part of the documentation of safe-use conditions</li> <li>• Any change to a Medication Guide that is an element of a REMS and for which FDA approval of the change is required<sup>b</sup></li> </ul>

*continued*

<sup>17</sup> See section IV., Submission Procedures.

***Contains Nonbinding Recommendations****Table 3, continued*

<b>Type of Change</b>	<b>Examples</b>
Major modifications that have a <i>substantial effect</i> on the actions applications holders, patients, health care providers, and other stakeholders must take to comply with the REMS	<ul style="list-style-type: none"> <li>• Removing or adding an element of the REMS</li> <li>• Substantially modifying an existing REMS element, including: <ul style="list-style-type: none"> <li>– Changes to the timetable for submission of assessments of the REMS that alter the frequency and/or number of the assessments</li> <li>– Changes to an ETASU<sup>c</sup> that modify the verification process required for the drug to be dispensed to patients</li> <li>– Adding a new letter to health professional societies to the REMS materials to describe new or clarified information about a serious risk</li> <li>– Adding/removing the REMS website from the communication plan or an ETASU</li> </ul> </li> <li>• Substantial changes to a REMS tool, including: <ul style="list-style-type: none"> <li>– Changing the prescriber enrollment form to add/remove an attestation that the prescriber understands the serious risk(s) of the drug</li> <li>– Extensive changes to a patient brochure to better educate patients about the serious risk(s) of the drug</li> <li>– Adding or removing a prescriber educational tool, such as a slide deck or safety information brochure</li> </ul> </li> <li>• Modification that proposes releasing the REMS requirement</li> <li>• Changing a REMS for an individual product to an SS REMS<sup>d</sup></li> </ul>

<sup>a</sup> See section V.F., REMS Modifications Included in Other Submissions.

<sup>b</sup> See 21 CFR 314.70(b)(2)(v)(B) and 601.12(f)(1). For a Medication Guide that is an element of a REMS, if the changes are required under section 505(o)(4) of the FD&C Act, the changes should be submitted in accordance with the procedures described in the guidance for industry *Safety Labeling Changes — Implementation of Section 505(o)(4) of the FD&C Act* (July 2013).

<sup>c</sup> ETASU = elements to assure safe use

<sup>d</sup> See the draft guidance for industry *Development of a Shared System REMS* (June 2018) for additional policies and procedures for modifying the REMS for an individual product to an SS REMS. When final, this guidance will represent the FDA's current thinking on this topic. For the most recent version of a guidance, check the FDA guidance web page at <https://www.fda.gov/regulatory-information/search-fda-guidance-documents>.

*Contains Nonbinding Recommendations***Table 4. REMS Modifications Due to Safety Labeling Changes (Type of Major Modification, Submitted as a PAS<sup>18</sup>)**

Type of Change	Examples
Changes that <i>are considered conforming</i> (i.e., modifications that transfer the newly approved labeling language into the existing REMS and/or REMS materials (60-day review))	<ul style="list-style-type: none"> <li>Updating language in the existing prescriber or pharmacy training materials to reflect approved safety labeling changes made to the WARNINGS and PRECAUTIONS sections of the package insert.</li> <li>Addition of newly approved language from the product labeling describing new adverse reactions and drug-drug interactions to the REMS patient education brochure</li> </ul>
Changes that <i>are not considered conforming</i> (i.e., overall programmatic and/or implementation changes to the REMS that result from approved (or ordered) safety labeling changes (180-day review))	<ul style="list-style-type: none"> <li>Addition of a new ETASU<sup>a</sup> requiring the documentation of safe-use conditions, based on the newly approved language in the BOXED WARNING and CONTRAINDICATIONS sections of the package insert</li> <li>Addition of a new Dear Health Care Provider Letter to the REMS materials that describes a new serious risk added to the product labeling</li> <li>Extensive changes to prescriber training materials to add new patient monitoring procedures necessary to address a new serious risk described in approved product labeling</li> </ul>

<sup>a</sup> ETASU = elements to assure safe use

#### IV. SUBMISSION PROCEDURES

This section provides an overview of submission procedures that apply to all REMS changes (revisions and modifications). The Appendix summarizes the relevant information that should be included in these submissions.<sup>19</sup>

<sup>18</sup> See section IV., Submission Procedures.

<sup>19</sup> The Electronic Submissions Gateway web page (<https://www.fda.gov/industry/electronic-submissions-gateway>) provides email addresses to which application holders can send questions about electronic submissions (e.g., location of REMS materials in the electronic common technical document) and general questions about sending electronic submissions through the electronic submissions gateway. Application holders also can refer to the guidance for industry *Providing Regulatory Submissions in Electronic Format — General Considerations* (January 1999).

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**A. General Considerations**

When the FDA requires a REMS change,<sup>20</sup> the FDA will describe the required change and the type of submission that is needed (CBE-30 supplement or PAS).

Application holders who wish to seek advice from the FDA before submission of a proposed REMS modification may do so in accordance with established FDA procedures.<sup>21</sup>

**B. Content and Format**

*1. Administrative Content*

Submissions should include:

- a) The appropriate submission identifier in bold capital letters at the top of the first page of the submission and completed Form FDA 356h (see the Appendix).
- b) A detailed description of the REMS changes to allow the FDA to determine quickly if the appropriate submission category has been used. This information can be included in the submission or the cover letter.
- c) A clean (without track changes) Word version of the changed REMS and REMS materials.
- d) A redlined (track changes) Word version of the changed REMS and REMS materials.
- e) One PDF file that includes a clean version of the changed REMS document and REMS materials.
- f) A clean (without track changes) Word version of the updated REMS Supporting Document<sup>22</sup> to align with changes made to the REMS document and REMS materials, as appropriate.

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<sup>20</sup> See section 505-1(g)(4)(B) of the FD&C Act.

<sup>21</sup> See the draft guidance for industry *Formal Meetings Between the FDA and Sponsors or Applicants of PDUFA Products* (December 2017) (when final, this guidance will represent the FDA's current thinking on this topic). Application holders seeking FDA advice about proposed modifications to REMS for drugs approved under an ANDA should contact the Office of Bioequivalence in the Office of Generic Drugs in CDER (see section VI., Contact Information).

<sup>22</sup> The REMS Supporting Document expands on information in the REMS document and provides additional information about the REMS, such as the rationale for, and supporting information about, the design, implementation, and assessment of the REMS. See the draft guidance for industry *Format and Content of a REMS Document* (October 2017). When final, this guidance will represent the FDA's current thinking on this topic. The statutory requirements for REMS revisions and modifications do *not* apply to the REMS Supporting Document (i.e., changes to the REMS supporting document are neither REMS revisions nor modifications).



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- g) A redlined (track changes) Word version of the updated REMS Supporting Document.
- h) A REMS history of all changes to the REMS since originally approved (see section IV.B.2., REMS History).
- i) **For REMS modifications only:** An adequate rationale for the proposed modifications (see section IV.B.3., Adequate Rationale for REMS Modifications).

## 2. *REMS History*

For all REMS changes, the FDA recommends application holders include a REMS history that outlines all changes made to the REMS since its original approval.

The REMS history should be similar in format to the history of labeling changes provided in submissions containing new labeling.<sup>23,24</sup> The REMS history should be in a tabular format that lists all approved and/or pending REMS changes with the approval or submission date, respectively, a summary of the changes (revisions and/or modifications), and a list of affected REMS materials.

## 3. *Adequate Rationale for REMS Modifications*

All proposed REMS modifications (minor or major) initiated by the application holder must include an *adequate rationale*.<sup>25</sup> The rationale may include, but is not limited to, the reason(s) why the proposed modification is necessary; the potential effect of the proposed modification on how the REMS addresses the serious risk(s) for which the REMS was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change. If a REMS assessment was submitted in the previous 18 months and includes data to support the proposed change, then it can be referenced as the adequate rationale.

When considering a proposed REMS modification as part of an efficacy supplement for a new indication for use (see section IV.C., Submission of Proposed REMS Changes), the REMS assessment that is required in accordance with section 505-1(g)(2)(A) of the FD&C Act will be considered the adequate rationale to support the proposed REMS modification. This adequate rationale should include:

<sup>23</sup> See the eCTD Technical Conformance Guide, Technical Specifications Document. This document is incorporated by reference in the guidance for industry *Providing Regulatory Submissions in Electronic Format — Certain Human Pharmaceutical Product Applications and Related Submissions Using the eCTD Specifications* (January 2019).

<sup>24</sup> For an example of a REMS history, see the draft guidance for industry *Use of a Drug Master File for Shared System REMS Submissions* (November 2017). When final, this guidance will represent the FDA's current thinking on this topic.

<sup>25</sup> See section 505-1(g)(4)(A) of the FD&C Act.



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- *In every case:* An evaluation of how the benefit-risk profile will or will not change with the new indication and the implications of any changes on the currently approved REMS
- *If the new, proposed indication for use introduces unexpected risks:* A description of those risks and an evaluation of whether those risks can be appropriately managed with the currently approved REMS
- *If the proposed REMS modification is based on a change in the benefit-risk profile or because of the new indication of use:* Explanation of the reason(s) why the proposed REMS modification is necessary; the potential effect of the proposed changes on how the REMS addresses the serious risk(s) for which the program was required, on patient access to the drug, and/or on the burden on the health care delivery system; and other appropriate evidence or data to support the proposed change
- *If a REMS assessment was submitted in the 18 months before submission of the supplemental application for a new indication for use:* A statement about whether the REMS was meeting its goals at the time of the last assessment and if any modifications of the REMS have been proposed since that assessment
- *If a REMS assessment was not submitted in the 18 months before submission of the supplemental application for a new indication for use:* Include as many of the currently listed assessment plan items as feasible

If the proposed REMS modifications are submitted in accordance with an FDA requirement to modify the REMS,<sup>26</sup> submission of an adequate rationale is not required as long as the proposed changes are identical to or consistent with those specified by the FDA. If the proposed REMS modification supplement includes changes that differ from the modifications described by the FDA, an adequate rationale is required for those proposed changes in accordance with section 505-1(g)(4)(A) of the FD&C Act.

If the proposed REMS modifications are due to approved safety labeling changes, or to safety labeling changes that the FDA has ordered the application holder to make, the adequate rationale can consist of a statement that the REMS changes are submitted due to the approved or ordered safety labeling changes (see section V.D., REMS Modification Due to Safety Labeling Changes).

### **C. Submission of Proposed REMS Changes**

Revisions should be submitted as “REMS Revision,” a submission type similar to drug correspondence. REMS revisions should be documented in the next annual report<sup>27</sup> and submitted at the time the revisions are implemented so that the current REMS document and

<sup>26</sup> See section 505-1(g)(4)(B) of the FD&C Act.

<sup>27</sup> A summary of REMS revisions should be included under section c of the next NDA, BLA, or ANDA annual report (21 CFR 314.81(b)(2)(iii)(c)).

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REMS materials are publicly displayed on the FDA web page of approved REMS.<sup>28,29</sup> Because REMS revisions are not submitted as supplemental applications, they do not require FDA action, and can be implemented following receipt by the FDA.

Proposed *minor* REMS modifications should be submitted as a CBE-30 supplement; proposed *major* modifications should be submitted as a PAS.

Proposed REMS modifications submitted to conform a REMS to approved or ordered safety labeling changes are major modifications and should be submitted as a PAS. However, these modifications are subject to a different time frame for review than other major modifications and safety labeling changes supplements submitted under section 505(o)(4) (see section V.D., REMS Modification Due to Safety Labeling Changes).

Application holders can submit multiple proposed REMS modifications of the same type (e.g., multiple minor modifications) in a single submission.

Application holders also can submit a single submission that contains REMS changes of different types (e.g., REMS revisions and minor (or major) modifications; or minor modifications and major modifications). However, a single submission with multiple REMS changes will affect the time frame for review of the submission (see section V.E., Submissions Containing More Than One Type of REMS Change).

A REMS assessment, supplemental efficacy application, or a supplemental CMC application may result in changes to an approved REMS.<sup>30</sup> REMS modifications included in these applications should include the relevant information for the submission and should be submitted according to the instructions described in the Appendix.

## **V. FDA TIME FRAMES<sup>31</sup> FOR REMS CHANGES**

The FDA will promptly assess submissions that contain proposed REMS changes to determine whether the proposed changes meet the criteria for the type of submission used (i.e., CBE-30 for minor REMS modifications or a PAS for major REMS modifications, including REMS modifications due to safety labeling changes). If the FDA determines that the REMS changes are not appropriately categorized and submitted, the FDA will notify the application holder, in

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<sup>28</sup> See section 505-1(h)(2)(C) of the FD&C Act.

<sup>29</sup> See the FDA web page Approved Risk Evaluation and Mitigation Strategies (REMS) — REMS@FDA, available at <https://www.accessdata.fda.gov/scripts/cder/remis/index.cfm>.

<sup>30</sup> Examples of REMS modifications that may result from efficacy supplements include addition of a new dosing regimen, or a new indication for use (see Tables 2 and 3). An example of a REMS modification that may result from a CMC supplement is addition of a new packaging to the REMS document and/or the appended REMS materials.

<sup>31</sup> The time frames described in this section refer to calendar days.

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writing, within 14 days of receipt of the submission, and as described in the following subsections.

**A. REMS Revisions**

REMS revisions are not submitted as supplemental applications; therefore, they do not require FDA action. Application holders can implement REMS revisions following receipt by the FDA.

**B. Minor REMS Modifications**

The FDA will review and act on proposed minor REMS modifications within 60 days of receipt.<sup>32</sup> Although the application holder can implement the modified REMS 30 days after receipt by the FDA, the changes to the REMS are not considered final until approved by the FDA.

If the FDA informs the application holder (within 14 days of receipt) that information necessary for the FDA to act on the submission is missing, the application holder should delay implementation. The missing information should be submitted as soon as possible, but no later than 10 days after notification. If the missing information is not received within 10 days of the FDA request, the FDA may issue a complete response letter.

**C. Major REMS Modifications**

The FDA will review and act on proposed major REMS modifications within 180 days of receipt.<sup>33</sup> Proposed major REMS modifications must not be implemented before FDA approval.<sup>34</sup>

**D. REMS Modification Due to Safety Labeling Changes**

The FDA will review and act on proposed *conforming REMS modifications* within 60 days of receipt and will review and act on *modifications not considered conforming* within 180 days of receipt. Proposed major REMS modifications, including modifications due to safety labeling changes, must not be implemented before FDA approval.<sup>35</sup>

The 60- or 180-day review time frame does not begin until the FDA receives the REMS modification to conform or align with the approved (or ordered) safety labeling changes. Even if

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<sup>32</sup> See section 505-1(h)(2)(A)(ii) of the FD&C Act.

<sup>33</sup> See section 505-1(h)(2)(A)(i) of the FD&C Act. The 180-day review time frame does not apply if the dispute resolution process described in section 505-1(h)(4) applies.

<sup>34</sup> See 21 CFR 314.70(b) and 21 CFR 601.12(b)(3) and (f)(1).

<sup>35</sup> See 21 CFR 314.70(b)(3). It is the FDA's view that the labeling changes process under 21 CFR 314.70 and 601.12 continues to be available to application holders in situations in which application holders become aware of newly acquired information, including in circumstances that meet the criteria for submission of a CBE-0.

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a REMS modification due to a safety labeling changes supplement is submitted at the same time as the corresponding proposed safety labeling changes, or after submission but before the approval of the labeling supplement (see section IV.C., Submission of Proposed REMS Changes), the 60- or 180-day review time frame does not begin until the associated labeling supplement is approved (or ordered)<sup>36</sup> and the REMS modification supplement is amended, if necessary, to accurately reflect the approved labeling.

**E. Submissions Containing More Than One Type of REMS Change**

Because the FDA takes one action per supplement, submissions that contain REMS changes of different types will be reviewed and acted on based on the time frame for the longer review clock. Therefore, the FDA will review and act on submissions that include both minor and major REMS modifications within 180 days of receipt (to allow sufficient time for review of the major modifications). The FDA will review and act on submissions containing both minor modifications and REMS revisions within 60 days (to allow sufficient time for review of the minor modifications).

**F. REMS Modifications Included in Other Submissions**

Proposed REMS modifications submitted with a REMS assessment required in accordance with the timetable for submission of assessments of the REMS will be reviewed concurrently with the REMS assessments. Action on the proposed REMS modifications will follow review of the REMS assessment.

Proposed REMS modifications submitted in an efficacy or CMC supplement will be reviewed and acted on as part of that supplement, and not according to the time frames described above.<sup>37</sup> REMS modifications submitted as part of an efficacy or CMC supplement may not be implemented until approved.

**G. Posting Revised and Modified REMS on the FDA Website**

The FDA intends to post updated REMS reflecting REMS revisions on the website within 14 days of receipt of the submission.<sup>38</sup>

The FDA intends to post updated REMS reflecting REMS modifications on the website within 3 days of approval.

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<sup>36</sup> See section 505-1(h)(2)(A)(iii) of the FD&C Act.

<sup>37</sup> For more information on the FDA's review of efficacy supplements, see the guidance for industry *Standards for the Prompt Review of Efficacy Supplements, Including Priority Efficacy Supplements* (May 1998). For more information on the FDA's review of CMC supplements, see the guidance for industry *Changes to an Approved NDA or ANDA* (April 2004).

<sup>38</sup> See <https://www.accessdata.fda.gov/scripts/cder/remis/>.

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**VI. CONTACT INFORMATION**

The contacts for questions about a proposed REMS revision or modification are as follows:

- **Center for Drug Evaluation and Research:**
  - For a drug under an NDA or BLA: the regulatory project manager in the Office of New Drugs review division responsible for that drug
  - For a drug under an ANDA: the REMS coordinator in the Office of Bioequivalence in the Office of Generic Drugs
  - For modifications of SS REMS: the regulatory project manager in the Project Management Staff, Office of Surveillance and Epidemiology
- **Center for Biologics Evaluation and Research:**
  - The regulatory project manager in the office responsible for that drug

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**APPENDIX:**  
**SUBMISSION PROCEDURES FOR CHANGES TO APPROVED REMS**

Table A summarizes the relevant information to include in submissions for changes (revisions and modifications) to approved risk evaluation and mitigation strategies (REMS).

**Table A: Information to Include in Submissions of Proposed REMS Changes**

<b>Type of REMS Change/ Submission Type</b>	<b>Submission Identifier</b>	<b>Instructions for Completing Form FDA 356h<sup>1</sup></b>	<b>Other Administrat ive Content<sup>2</sup></b>	<b>REMS History<sup>3</sup></b>	<b>Adequate Rationale<sup>4</sup></b>
REMS Revision	<b>REMS REVISION</b>	<b>Field 21</b> – Select “Other” and enter “REMS Revision”  <b>Field 25</b> – Enter “REMS Revision”	Items <sup>5</sup> b-h	Recommended	Not required
Minor REMS Modification	<b>NEW SUPPLEMENT FOR [NDA/BLA/ ANDA]<sup>6</sup> [assigned #]</b>  <b>CHANGES BEING EFFECTED IN 30 DAYS</b>  <b>PROPOSED MINOR REMS MODIFICATION</b>	<b>Field 21</b> – Select “REMS Supplement”  <b>Field 23</b> – Select “CBE-30”  <b>Field 25</b> – Enter “Proposed Minor REMS Modification”	Items b-i	Recommended	Required

*continued*

*Contains Nonbinding Recommendations**Table A, continued*

<b>Type of REMS Change/ Submission Type</b>	<b>Submission Identifier</b>	<b>Instructions for Completing Form FDA 356h<sup>1</sup></b>	<b>Other Administrat ive Content<sup>2</sup></b>	<b>REMS History<sup>3</sup></b>	<b>Adequate Rationale<sup>4</sup></b>
Major REMS Modification	<b>NEW SUPPLEMENT FOR [NDA/BLA/ANDA ] [assigned #]  PRIOR APPROVAL SUPPLEMENT  PROPOSED MAJOR REMS MODIFICATION</b>	<b>Field 21</b> – Select “REMS Supplement”  <b>Field 23</b> – Select “Prior Approval (PA)”  <b>Field 25</b> – Enter “Proposed Major REMS Modification”	Items b-i	Recommended	Required
REMS Modification Due to Safety Labeling Changes  (Major REMS Modification)	<b>NEW SUPPLEMENT FOR [NDA/BLA/ANDA ] [assigned #]  PRIOR APPROVAL SUPPLEMENT  PROPOSED REMS MODIFICATIONS DUE TO SAFETY LABELING CHANGES SUBMITTED IN SUPPLEMENT [supplement #]</b>	<b>Field 21</b> – Select “REMS Supplement”  <b>Field 23</b> – Select “Prior Approval (PA)”  <b>Field 25</b> – Enter “Proposed REMS Modification Due to Safety Labeling Changes Submitted in Supplement [supplement #]”	Items b-i	Recommended	Required

*continued*

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<b>Type of REMS Change/ Submission Type</b>	<b>Submission Identifier</b>	<b>Instructions for Completing Form FDA 356h<sup>1</sup></b>	<b>Other Administrat ive Content<sup>2</sup></b>	<b>REMS History<sup>3</sup></b>	<b>Adequate Rationale<sup>4</sup></b>
Multiple Types of REMS Changes in Same Submission	<b>NEW SUPPLEMENT FOR [NDA/BLA/ANDA ] [assigned #]</b>  <b>PRIOR APPROVAL SUPPLEMENT</b>  <b>OR CHANGES BEING EFFECTED IN 30 DAYS</b>  <b>PROPOSED REMS MODIFICATIONS</b>	<b>Field 21</b> – Select “REMS Supplement”  <b>Field 23</b> – Select “Prior Approval (PA)” <u>or</u> “CBE- 30”  <b>Field 25</b> – Enter “Proposed REMS Modification”	Items b-i	Recommended	Required

*continued*



*Contains Nonbinding Recommendations**Table A, continued*

<b>Type of REMS Change/ Submission Type</b>	<b>Submission Identifier</b>	<b>Instructions for Completing Form FDA 356h<sup>1</sup></b>	<b>Other Administrat ive Content<sup>2</sup></b>	<b>REMS History<sup>3</sup></b>	<b>Adequate Rationale<sup>4</sup></b>
Efficacy Supplement With Proposed REMS Modifications	<p><b>NEW SUPPLEMENT FOR [NDA/BLA] [assigned #]</b></p> <p><b>PRIOR APPROVAL SUPPLEMENT</b></p> <p>&lt; other supplement identification &gt;</p> <p><b>[EFFICACY SUBMISSION CONTENT INFORMATION]</b></p> <p><b>PROPOSED REMS MODIFICATION</b></p>	<p><b>Field 21</b> – Select “Efficacy Supplement” <b>and</b> “REMS Supplement”</p> <p><b>Field 23</b> – Select “Prior Approval (PA)”</p> <p><b>Field 25</b> – Enter “Efficacy Supplement” <b>and</b> “Proposed REMS Modification”</p>	Items b-i	Recommended	Required

*continued*

*Contains Nonbinding Recommendations**Table A, continued*

Type of REMS Change/ Submission Type	Submission Identifier	Instructions for Completing Form FDA 356h <sup>1</sup>	Other Administrat ive Content <sup>2</sup>	REMS History <sup>3</sup>	Adequate Rationale <sup>4</sup>
CMC <sup>6</sup> Supplement With Proposed REMS Modifications	<p align="center"><b>NEW SUPPLEMENT FOR [NDA/BLA/ANDA ] [assigned #]</b></p> <p align="center"><b>PRIOR APPROVAL SUPPLEMENT or CHANGES BEING EFFECTED in 30 Days</b></p> <p align="center">&lt; other supplement identification &gt;</p> <p align="center"><b>[CMC SUBMISSION CONTENT INFORMATION]</b></p> <p align="center"><b>PROPOSED REMS MODIFICATION</b></p>	<p><b>Field 21</b> – Select “CMC Supplement” <b>and</b> “REMS Supplement”</p> <p><b>Field 23</b> – Select “CBE-30” <b>or</b> “Prior Approval (PA)”</p> <p><b>Field 25</b> – Enter “CMC Supplement <b>and</b> “Proposed REMS Modification”</p>	Items b-i	Recommended	Required

*continued*

***Contains Nonbinding Recommendations****Table A, continued*

<b>Type of REMS Change/ Submission Type</b>	<b>Submission Identifier</b>	<b>Instructions for Completing Form FDA 356h<sup>1</sup></b>	<b>Other Administrat ive Content<sup>2</sup></b>	<b>REMS History<sup>3</sup></b>	<b>Adequate Rationale<sup>4</sup></b>
REMS Assessment With Proposed REMS Modifications	<b>NEW SUPPLEMENT FOR [NDA/BLA/ANDA ] [assigned #]</b>  <b>PRIOR APPROVAL SUPPLEMENT or CHANGES BEING EFFECTED in 30 Days</b>  <b>REMS MODIFICATION/ REMS ASSESSMENT</b>	<b>Field 21</b> – Select “REMS Supplement” <b>and</b> “Other”; then enter “REMS Assessment”  <b>Field 23</b> – Select “CBE-30” <b>or</b> “Prior Approval (PA)”  <b>Field 25</b> – Enter “REMS Assessment” <b>and</b> “Proposed REMS Modification”	Items b-i	Recommended	Required: The required REMS assessmen t included with the supplemen t is considered the adequate rationale

<sup>1</sup> The field numbers in this column correspond to the number boxes on Form FDA 356h.<sup>2</sup> See section IV.B.1., Administrative Content, of the guidance.<sup>3</sup> See section IV.B.2., REMS History, of the guidance.<sup>4</sup> See section IV.B.3., Adequate Rationale for REMS Modifications, of the guidance.<sup>5</sup> Items as listed in section IV.B.1., Administrative Content, of the guidance.<sup>6</sup> NDA = new drug application; BLA = biologics license application; ANDA = abbreviated new drug application; CMC = chemistry, manufacturing, and controls